CHAPTER 2

Review of Literature
# CHAPTER-2

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Chapter-2: Review of literature

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<th>Page No.</th>
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2. Literature review of hydrazone derivatives: synthesis, biological activity and applications of substituted hydrazones

2.1 Introduction to substituted hydrazones

Compounds containing general formula of ArCONHN\(=\)C(R) Ar’ are known as N-acyl hydrazones. Hydrazones contains an azomethine CO-NH-N=CH group which plays a vital role in the biological activity. They are generally prepared by reacting acid hydrazide with aldehydes or ketones either in solvent free conditions or in various solvents. As mentioned in the introduction chapter the acyl hydrazone derivatives can exist in four possible forms due to the presence of the azomethine group. The acylhydrazones will exhibit geometrical isomerism (syn and anti) due to the presence of the double bond between C and N. The study of the isomers has become very vital to synthesize particular isomers which may have some crucial role in the bioactivity of the acyl hydrazones.

The present chapter is emphasized on the literature survey of the natural occurrence, medicinal importance, utility and synthesis of various substituted acyl hydrazones of pharmaceutical importance. In the realm of nitrogen containing molecules, acyl hydrazones has occupied a prominent class that are having versatile chemical reactivity precursors and intermediates of various essential organic molecules such as polymers, pharmaceuticals and heterocycles. Acylhydrazones are widely explored in the recent years and are found to have broad range of biological properties and analytical properties. Due to their feasibility in the synthesis an enormous variety of the
chemical libraries were constructed for various innovation of pharmacological molecules.\textsuperscript{13-20}

**2.2 Synthesis of substituted hydrazones**

The common and traditional method for preparation of the NAHs involves the treatment of substituted acid hydrazides and carbonyl compounds in the suitable solvents. All the reported approaches include organic classical synthetic methodologies and vary in the selectivity and reaction patterns. A wide variety of methodologies has been developed by the researchers in past decades. Some of the reported methods are described below.

M. C. Witschel \textit{et al.} prepared a series of 1,3-diiminoisoindoline carbohydrazides by treating the ethyl ester with hydrazine and the corresponding hydrazide derivatives to synthesized isoindoline in ethanol as per the below mentioned scheme and the obtained compounds were found to be potent inhibitors of \textit{P. Falciparum} proliferation in red blood cells.\textsuperscript{21}

\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} & \quad \text{O} \\
\end{align*}

\text{EtOH} \quad \text{EtOH}

\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\end{align*}

\text{Scheme.2.1}
Abadi et al. synthesized a series of analogues of pyrazole with 1,3,4-substitution as per the below given scheme and all derivatives were evaluated for their anti-angiogenic and anti-tumor properties.\textsuperscript{22}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\includegraphics[width=0.8\textwidth]{scheme.png}};
  \node[below right,align=left] at (A) {\textbf{Scheme.2.2}};
\end{tikzpicture}
\end{center}

A series of novel hydrazone derivatives containing furoxan ring has been prepared by Nguyen Huu Dinh and his co workers. As per their method isoeugenoxyacetic acid was used as the key starting material for the preparation of all the derivatives as per the below mentioned scheme. Among the prepared hydrazide-hydrazones derivatives few products were exhibited inhibition activities \textit{in vitro} on human epidermis carcinoma (KB-cell) with IC\textsubscript{50} = 47, 68, 79, and 103 mg/mL.\textsuperscript{23}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\includegraphics[width=0.8\textwidth]{scheme2.png}};
  \node[below right,align=left] at (A) {\textbf{Scheme.2.3}};
\end{tikzpicture}
\end{center}

A. F. Maria and co workers prepared a new series of carbohydrazide derivatives using phenyl pyrazole carboxaldehyde as
the starting material. The pyrazole carboxaldehyde was converted to the corresponding CONHNH₂ derivative and then subsequently reacted with appropriate aldehydes in the ethanol to obtained the corresponding hydrazine-hydrazides.²⁴

![Scheme 2.4](image)

Scheme 2.4

Mostafa M. Ghorab et al. synthesized a library of novel hydrazide chromene and benzochromene derivatives as per the scheme shown below. 2-Cyano-N[1(substitutedphenyl)ethylidene]acetohydrazide 3 was obtained by coupling of acetophenone derivative 1 with hydrazide derivavative of cyanoacetic acid 2. The obtained compound 3 was reacted with different aldehydes in dioxane, catalytic amount of piperidine to produce chromene and benzochromene derivatives 4, 5 through the new cyclization reactions.²⁵
S. Sadjadi et al. reported the preparation of N-acyl-benzoyl hydrazone and benzoyl hydrazone derivatives in the presence of different types keggin type of heteropolyacids like H₃[PMo₁₂O₄₀], H₄[PMo₁₁VO₄₀], H₅[PMo₁₀V₂O₄₀], and H₆[PMo₉V₃O₄₀] as catalyst in the acetonitrile solvent. Reaction mixture was filtered to recycle the catalyst.²⁶
Jie Zhang and his coworkers prepared new derivatives of hydrazide-hydrazone by reacting the compound $1$ with hydrazine hydrate in the presence of catalytic amount of $\text{H}_2\text{SO}_4$ in the solvent, the obtained hydrazide reacted with required carbonyl compounds to get the compound $3$ using catalytic amount of acetic acid. $^{27}$

![Scheme-2.7](image)

**Scheme-2.7**

A new library of N-acylhydrazones was synthesized by V.K Pandy *et al*, by refluxing the appropriate aromatic aldehydes with acid hydrazides in glacial acetic acid. The product was precipitated by pouring the reaction mixture in methanol and the isolated compound was purified further by ethanol to get the desired purity.$^{28}$

![Scheme-2.8](image)

**Scheme-2.8**

Bukowski and his co workers, reported a series of hydrazone compounds by refluxing the compound $2$ with compound $1$ in presence of the catalytic quantity of piperidine.$^{29}$
Scheme 2.9

A novel series of mefenamic acid N-aryl hydrazone derivatives were prepared by Almasirad et al, as per the below scheme. A mixture of aldehyde and hydrazide were treated in ethanol at 30°C in the presence of the conc. HCl as catalyst.³⁰

Scheme 2.10

Lehmann Jand his co worker prepared the compound 4 by aging the 2-indole carbohydrazide for three hours at room temperature in ethanol.³¹ The compound was also obtained by condensing 1 with the aldehyde 3.

Scheme 2.11

Nasr and his co-workers synthesized a new library of sydnone derivatives by converting acid to hydrazide in the presence of DCC,
followed by converting it in to corresponding hydrazone derivatives by reacting with appropriate aldehyde in ethanol.\textsuperscript{32}

\textbf{Scheme.2.12}

A new NAHs were synthesized by Olsson and his team as per the below scheme. The hydrazide intermediate was formed by treating ester with hydrazine hydrate under the microwave conditions. The formed hydrazide was treated with bromoacetophenone to afford the final product. The isolated product was found to act as a selective nonpeptidic and potent PAR-2 agonists.\textsuperscript{33}

\textbf{Scheme.2.13}

D. Kumar \textit{et al.} prepared hydrazide hydrazones derivatives by treating the phenyl glyoxals with the phenyl hydrazides in acetonitrile at room temperature for 3 hours to afford the hydrazone derivatives.\textsuperscript{34}
A series of acyl hydrazones were synthesized from the hydrazides and aldehydes that are commercially available. The hydrazides are treated with appropriate aldehydes in the DMF at room temperature to get the corresponding hydrazone derivatives.\(^\text{35}\)

**Scheme-2.15**

Substituted NAHs show a diverse biological activity, such as anti-tumoral, schistomiasis, analgesic, anti-tubercular, anti-inflammatory, anti-microbial, anti-convulsant and anti-platelet activities.\(^\text{36,37}\)

Isonicotinic acid hydrazide (INH) or isoniazid was discovered as the anti-tuberculosis agent in 1912 and used as medication in the treatment. Isoniazide also displayed anti depressant activity and it has showed excellent inhibition in opposition to *mycobacterium tuberculosis*.

Hydrazones exhibit less toxic activity than hydrazides due to the blockage of −NH\(_2\) group. These prior findings support the immense importance of the synthesis of NAH in the pharmaceutical field.\(^\text{38-40}\)
4-Hydroxy-\(N'-(5\text{-nitrofuran-2-yl})\) methylene benzohydrazide, Nifuroxazide (INN) is an oral hydrazone based heterocyclic antibiotic used for the treatment of diarrhea and colitis. Few examples are given below.

**2.3a Vasodilator activity**

Silva and his co workers prepared a new class of thienyl substituted hydrazone derivatives. The final compounds were found to display the vasodilator property.\(^\text{41}\)

![Fig.2.1](image)

**2.3b Anti-tumoral activity**

A large number of anti-tumoral drugs presently exist in the pharmaceuticals, the innovations for the antitumor medicines lead to the findings of many substituted hydrazones which contains anti-tumoral property. Few of the hydrazones having diphenolic groups has shown uterotrophic inhibition up to 70%, the compound shown below displayed the cytotoxicity activity (from 50-70%) on human malignant breast cell lines ZR-75-1 and MCF-7.\(^\text{42}\) Some of the examples which exhibit the antitumor activity are depicted in table **2.3.1**.
Table 2.1: substituted hydrazones with antitumor activity

<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Compound 1" /></td>
<td>Antitumor</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>R = 2-HOC₆H₄, 4-HOC₆H₄, 4-H₂NC₆H₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Compound 2" /></td>
<td>Anti-tumor</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Compound 3" /></td>
<td>Anti-cancer</td>
<td>45</td>
</tr>
<tr>
<td>S. No</td>
<td>Compound</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Compound 4" /></td>
<td>Anti-cancer</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2.png" alt="Compound 5" /></td>
<td>Anti-cancer</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3.png" alt="Compound 6" /></td>
<td>Anti-cancer</td>
<td>48</td>
</tr>
</tbody>
</table>

**2.3c Anti-convulsant activity**

Anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epilepsy. Epilepsy is a general neurological disorder and a common term given to a group of syndromes that involve abnormal and spontaneous, electrical activity, in the brain. Anticonvulsants also prevent the spread of the seizure within the brain. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers, and for the treatment of neuropathic pain.

Dimmock and his co-workers prepared a series of acetyl hydrazones, and among them the following hydrazone showed
prominent anticonvulsant activity. Some of the NAHs examples are given in below table.

![Fig. 2.3](image)

**Table.2.2: Hydrazones with anticonvulsant activity**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Compound 1" /></td>
<td>Anti-convulsant</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Compound 2" /></td>
<td>Anti-convulsant</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Compound 3" /></td>
<td>Anti-convulsant</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Compound 4" /></td>
<td>Anti-convulsant</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Compound 5" /></td>
<td>Anti-convulsant</td>
<td>54</td>
</tr>
</tbody>
</table>
2.3d Analgesic and anti-inflammatory activity

Anti-inflammatory drugs are the substances that are used in the treatment of inflammation and also act as analgesic by reducing the pain. Non-steroidal anti-inflammatory drugs (NSAIDs) possess a diverse clinical use for the treatment of inflammatory and conditions including oral cavity lesions, rheumatoid arthritis and respiratory tract infections.

A new series of the hydrazone derivatives was synthesized by the Bouzidi et al, by identifying through the docking filters and all the target compounds were evaluated in vivo in a model of neuropathic pain, the compound showed the prominent anti-analgesic behavior\textsuperscript{55}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig2.png}
\caption{Fig. 2.4}
\end{figure}

<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Anti-inflammatory</td>
<td>56</td>
</tr>
<tr>
<td>S. No</td>
<td>Compound</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Compound 2" /></td>
<td>Analgesic and anti-inflammatory</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Compound 3" /></td>
<td>Analgesic and anti-inflammatory</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Compound 4" /></td>
<td>Analgesic</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Compound 5" /></td>
<td>Analgesic</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Compound 6" /></td>
<td>Analgesic and anti-inflammatory</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Compound 7" /></td>
<td>Analgesic and anti-inflammatory</td>
<td>62</td>
</tr>
<tr>
<td>S. No</td>
<td>Compound</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>8</td>
<td><img src="images/compound8.jpg" alt="Chemical Structure" /></td>
<td>Analgesic</td>
<td>63</td>
</tr>
</tbody>
</table>

### 2.3e Anti-platelet activity

Anti-coagulant and anti-platelets are a class of drugs that work by stopping platelets from adhering to one another and clotting proteins from binding together and thus inhibits the thrombus formation. They are widely used in primary and secondary prevention of thrombotic cerebrovascular or cardiovascular disease.

Lima and his co-workers prepared arylsulfonate acylhydrazone derivatives as a new class of antiplatelet drug candidates which exhibited prominent antithrombotic activity. Among the series the compound 1 exhibited antiplatelet activity by inducing the thrombin by involving TXA2 formation, compound 2 selectively inhibited the platelet aggregation.\textsuperscript{64} Few examples are tabulated below.

![Fig. 2.5](images/fig2_5.png)

![Fig. 2.6](images/fig2_6.png)
Table.2.4: Substituted hydrazones with anti-platelet activity

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Anti-platelet Activity</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Anti-platelet Activity</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Anti-platelet Activity</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Anti-platelet Activity</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Anti-platelet Activity</td>
<td>69</td>
</tr>
</tbody>
</table>

2.3f Anti-microbial activity

Antimicrobial are the agents, inhibits the growth of the microorganisms like bacteria and fungi. In the recent decades the
necessity to develop new anti-microbial drugs has been increased due to the prevalence of new microbial infections.

Bhavesh and his coworkers prepared a new series of the isatin derivatives, the prepared targets were tested for the anti-microbial activity using the disk diffusion technique. Among the compounds, the compounds having 5-Cl, 5-I substitution showed high antimicrobial activity. Some of the examples are tabulated below.

![Image of substituted hydrazones]

**Fig. 2.7**

**Table 2.5: Substituted hydrazones with anti-microbial activity**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image of compound]</td>
<td>Anti-bacterial and anti-fungal</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>![Image of compound]</td>
<td>Anti-bacterial</td>
<td>72</td>
</tr>
<tr>
<td>S.No</td>
<td>Compound</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Compound 3" /></td>
<td>Anti-bacterial</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Compound 4" /></td>
<td>Anti-bacterial</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Compound 5" /></td>
<td>Anti-bacterial and anti-fungal</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Compound 6" /></td>
<td>Anti-fungal</td>
<td>76</td>
</tr>
</tbody>
</table>

2.4 Synthetic use of N-acyl substituted hydrazones as intermediates

Apart from their significant biological activity the NAHs can be used as the intermediates in the preparation of several heterocyclic drug moieties which possess important biological activities. Many NAHs can be easily prepared, can be obtained as solids in the pure
form and they can be stored for long term. This property made them to use as starting materials in various reactions like: formation of variety of thiazolidinone derivatives, \textsuperscript{77,78} N-alkylhydrazides, \textsuperscript{79} oxadiazolines \textsuperscript{80-82} and azetidinones. \textsuperscript{83}

John H. Museer and his coworkers prepared a series of benzo heterocycles according to the below given scheme, \textsuperscript{84} the newly synthesized compounds exhibited anti-allergic nature. The compound terephthalide 1 reacted with appropriate carbohydrazides in ethanol, in the reflux condition to afford the corresponding bis(carbohydrazones). The obtained carbohydrazones derivatives 2 were refluxed in acetic acid/ethanol mixture to afford the bis(dihydrooxadiazolyl)benzene derivatives 3.

\begin{center}
\textbf{Scheme. 2.16}
\end{center}

NAHs on allylation gives the homoallylic derivatives of hydrazides, this reaction can be accomplished by Lewis acid as catalyst by tetra allyltin derivatives. Many functional groups remain intact in this reaction conditions.\textsuperscript{85}
Reaction of indole carbohydrazide

Scheme 2.17

Derek H. R. Barton and his co-workers synthesized a series of pyrazidine derivatives by substituted hydrazones as per the below mentioned scheme.\textsuperscript{86} Reaction of indole carbohydrazide 1 with aromatic aldehydes gave the corresponding hydrazone derivatives 2 which on treatment with acetyl chloride, resulted in the formation of interesting tricyclic indolo[2,3-d]pyridazine derivatives 3.

Scheme 2.18

NAHs can also participate in the intra and intermolecular [4+2] Diels-Alder cycloaddition reactions, they can act as azadines in the reaction to produce the cyclic derivatives at elevated temperatures.\textsuperscript{87}

Scheme 2.19
N-Acyl hydrazones give only N-alkylhydrazines according to the below scheme by using sodium borohydride catalyzed by Raney Ni. The reactions were carried out in methanolic NaOH solutions, and the required products were obtained in high to moderate yields.  

![Scheme 2.20](image)

Arylidine hydrazones on cyclocondensation with thioacetic acid and thioglycolic acid gives derivatives of thiazolidinone and thiazolidinediones respectively.

![Scheme 2.21](image)

Zhenhua Shaang converted aromatic N-acylhydrazones to 2,5-disubstituted 1,3,4-oxadiazoles by oxidizing them with bis (trifluoroacetoxoy)iodobenzene. \(^\text{90}\) N-acylhydrazone 1 was taken in DMSO in the presence of bis(trifluoroacetoxoy)iodobenzene 2 and stirred at room temperature. After completion of the reaction, flash column purification of the product afforded the desired product.

![Scheme 2.22](image)
Benzoic acid substituted hydrazone derivatives in the presence of thionyl chloride and phenoxy acetic acid undergo cyclization to give the corresponding azetidinone derivatives.\textsuperscript{91}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) \[ \text{Ar} \text{N} \text{N} \text{Ar} \text{PhOCH}_2\text{COOH} \rightarrow \text{Ar} \text{N} \text{N} \text{Ar} \text{OPh} \]
; \node (B) at (2,0) {\textbf{Scheme.2.23}};
\end{tikzpicture}
\end{center}

Selective N-alkylhydrazines can be produced by reducing the N-acyl hydrazones with milder reducing reagents like sodium borohydride.\textsuperscript{92}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) \[ \text{Ar} \text{N} \text{N} \text{Ar} \rightarrow \text{Ar} \text{N} \text{N} \text{Ar} \text{SBH} \]
; \node (B) at (2,0) {\textbf{Scheme.2.24}};
\end{tikzpicture}
\end{center}

NAHs on hydro cyanation lead to the formation of α-hydrazino acids in the presence of sodium cyanide and phase transfer catalyst. Hydrogen cyanide generated \textit{in-situ} which facilitates the reaction.\textsuperscript{93}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) \[ \text{R}_1 \text{N} \text{NHCOR}_3 + \text{NaCN} \rightarrow \text{HNHCOR}_3 \text{NHCOR}_3 \text{R}_1 \text{R}_2 \text{H}_2 \text{O/Hexane} \]
; \node (B) at (2,0) {\textbf{Scheme.2.25}};
\end{tikzpicture}
\end{center}